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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/553,368	04/20/00	ILL	C TTI-180DV

000959  
LAHIVE & COCKFIELD  
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BOSTON MA 02109

HM12/1001

EXAMINER

SCHNIZER, H

ART UNIT

PAPER NUMBER

1653

DATE MAILED: 10/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

**FILE COPY**

Application No.

09/553,368

Applicant(s)

ILL ET AL.

Examiner

Holly Schnizer

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on 20 October 2000.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 40-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 40-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☒ Certified copies of the priority documents have been received in Application No. 09/205,817.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 and 7. 6) ☐ Other: \_\_\_\_\_

Art Unit: 1653

## **DETAILED ACTION**

### ***Status of the Claims***

The Preliminary Amendment of Paper No. 21 has been entered. Claims 1-39 have been cancelled. Claims 40-56 are pending and will be examined on the merits in this Office Action.

### ***Drawings***

The Drawings filed April 20, 2000 have been objected to by the draftsman for reasons cited on the attached Form PTO-948. Correction is required.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 40-47 and 49-56 are rejected under 35 U.S.C. 102(a) as being anticipated by Ill et al. (Blood Coagulation and Fibrinolysis (Dec. 1997) 8(suppl. 2): S23-S30; ref. B7 of IDS of Paper No. 4).

Art Unit: 1653

III et al. teach an expression vector comprising the human thyroid binding globulin promoter, the alpha-1 microglobulin/bikunin enhancer, and a leader sequence that comprises an intron with a 5'donor site and a consensus 3'splice acceptor site all of which are upstream of the coding sequence for B-domain deleted factor VIII (p. S24, Col. 1, "Plasmids" and p. S25, Figure 1). III et al. indicate that the intron is located downstream of the promoter and enhancer but upstream of the coding sequence (Figure 1). Since introns can increase the stability of mRNA, it appears that the III et al. reference anticipates Claim 49. One of the constructs taught by III et al. contains two copies of the enhancer (Table I and p. 25, Col. 2, last paragraph).

Claims 40-47 and 49-56 are rejected under 35 U.S.C. 102(a) as being anticipated by III et al. (Thrombosis & Hemostasis, (July 1997) ISSN: 0340-6245; ref. B8 of IDS of Paper No. 4).

It appears that the abstract by III et al. is related to the full length publication discussed in the rejection above therefore, for the reasons stated above and repeated here, the claims are unpatentable over III et al.

III et al. teach an expression vector comprising the human thyroid binding globulin promoter, the alpha-1 microglobulin/bikunin enhancer, and a leader sequence that comprises an intron with a 5'donor site and a consensus 3'splice acceptor site all of which are upstream of the coding sequence for B-domain deleted factor VIII . III et al. indicate that the intron is located downstream of the promoter and enhancer but upstream of the coding sequence (Figure 1). Since introns can increase the stability of

Art Unit: 1653

mRNA, it appears that the Ill et al. reference anticipates Claim 49. One of the constructs taught by Ill et al. contains two copies of the enhancer.

Claims 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Gould et al. (J. Cell Biochem. (1990) Suppl. 14A, D432).

Gould et al. teach an expression vector comprising the albumin liver specific promoter (line 6 of abstract) and the alpha-fetaprotein enhancer sequence (line 7 of abstract) both of which are located upstream from the coding sequence of the gene. Therefore, it appears that Gould et al. meets the limitations of Claims 40-41.

Claims 40, 41, and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Simonet et al. (U.S. Patent No. 6,268,212).

Simonet et al. teach an expression vector comprising the liver specific albumin promoter and the liver specific HCR enhancer upstream from the coding sequence (see Col. 2, lines 12-37, claim 1). Simonet et al. also teach placement of an intron downstream from the promoter and enhancer and upstream from the coding sequence (see Figure 2A wherein HCR is the enhancer, ApoE contains the promoter and intron, and IL-8 is the coding sequence).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40, 41, 42, 45, 47, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Connelly et al. (Human Gene Therapy (1996) 7: 183-195) in view of Simonet (U.S. Patent No. 6,268,212).

Connelly et al. teach an expression vector comprising the albumin liver specific promoter upstream of the coding sequence for the B-domain deleted factor VIII. Connelly et al. also teach the placement of an intron downstream of the promoter and upstream of the coding sequence.

Connelly et al. do not teach that the expression vector contains a liver specific enhancer.

Simonet teaches an expression vector comprising a liver specific promoter, such as albumin, and the liver specific enhancer, HCR (hepatocyte control region) (see Claim 1 of Simonet). Simonet et al. also teach placement of an intron downstream from the promoter and enhancer and upstream from the coding sequence (see Figure 2A wherein HCR is the enhancer, ApoE contains the promoter and intron, and IL-8 is the coding sequence). Insertion of introns into expression vectors is thought to increase stability of the mRNA transcribed from the gene.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the expression vector of Connelly et al. to include a liver specific enhancer such as the HCR enhancer taught in Simonet. Connelly et al. indicates that there is a need in the art to increase expression and liver specificity of factor VIII (see p. 184, Col. 1). Connelly et al. indicate that obtaining liver specificity at the transcriptional level could be achieved by inclusion of regulatory elements or a liver-specific promoter into the expression vector disclosed therein (p. 184, Col. 1, last 7 lines of second paragraph). Connelly et al. show that insertion of a liver specific albumin promoter resulted in high level expression of the B-domain deleted Factor VIII specifically in liver cells. One of skill in the art would have looked to Simonet to improve on the expression vector of Connelly et al. since Simonet indicates that the HCR enhancer is functional with the albumin promoter (the promoter used in the Connelly et al. vector)(Col. 7, lines 26-32), the HCR enhancer can confer a significant degree of liver specific expression of a transgene and can increase the level of expression of a transgene in the liver (Col. 5, lines 42-45). Thus, it appears that the claims are unpatentable over the prior art.

Art Unit: 1653

**Conclusions**


No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Holly Schnizer  
September 24, 2001

  
CHRISTOPHER S. F. LOW  
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